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Testicular Size and Shape of 47,XYY and 47,XXY Men in a Double-Blind, Double-Matched Population Survey

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SUMMARY

This paper reports the testicular size and shape of 12 men with 47,XYY, 14 men with 47,XXY, and 52 matched controls with 46,XY. The abnormal karyotypes were identified in a systematic population search for XYY and XXY men. The subjects and their matched controls were examined in a double-blind fashion.

The testes of the XYY men showed no significant differences from those of their XY controls for volume or shape. This indicates that previous reports of abnormal testes in XYYs reflect selection and publication bias and do not provide an accurate description of the condition of 47,XYY men's testicles.

As expected, the testes of the XXY men were significantly smaller than those of their XY controls, and there was also a difference in shape. However, the mean size in this sample of XXYs was larger than in previous reports on Klinefelter syndrome patients, indicating that previous reports on XXYs, identified in clinics for male hypogonadism and other institutions, also suffered from selection bias.

INTRODUCTION

This paper deals with the testicular size, shape, and condition of men with abnormal sex chromosome complements 47,XYY and 47,XXY. The subjects were found in an unbiased population survey. Testicular size and condition in 47,XYY men has been reported many times since this anomaly was first described [1]. However, nearly all

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reports have described subjects identified in some type of institution. Few investigators have attempted population studies.

Abnormal testicular size in 47,XYY males was reported in a large proportion of cases published from 1961 to 1975 [2–13]. Other studies considered 47,XXY testicular size to be within normal limits [9–12, 14–16], but few subjects were actually measured. In addition, Skakkebæk [17] found abnormal seminiferous epithelium in biopsies from 11 of 14 XYYs. Since these case reports were not obtained from unbiased population studies, the possibility of selection bias leaves the question of testicular size in XYYs unclear.

Descriptions of Klinefelter syndrome have invariably included small testicles along with the three classical signs: gynecomastia, aspermatogenesis without Leydig cells, and increased excretion of FSH. These patients usually have an XXY sex chromosome constitution [18, 19]. Subsequently, the 47,XXY karyotype has been incorporated into the definition of "true" Klinefelter syndrome. Since Klinefelter et al. [20] reported small testes in the initial description of this syndrome, reports on another 180 XXYs have indicated small testis with lengths under 2.6 cm in 179 cases [21–24].

MATERIALS AND METHODS

The starting population for this study consisted of the 31,436 men born in 1944–1947 whose mothers were registered inhabitants of Copenhagen when they gave birth. The height of each man surviving to adulthood was noted, and buccal smears and blood samples were collected from 4,139 men who reached adult heights of 184 cm or more. Details of this case-finding procedure are provided elsewhere [25, 26].

In this way, 12 XYY and 16 XXY men were identified. All of the XYYs and 14 of the XXYs, together with two groups of matched control XY subjects, also selected from the set of 4,139 men, agreed to an intensive two-day double-blind examination. One group of controls (control-1) was matched for age, height, and the social class of their parents when the subject was born. A second group (control-2) was matched for age, height, parents' social class, plus performance on an intelligence test (to control for the intelligence level of the XYY and XXY subjects). All 78 participants were from 26 to 31 years at the time of the testicular examination.

The testes were measured with a Lange caliper while the subject was standing. All three dimensions (height, small width, and large width) were taken with the caliper in the right hand and the testicle held between the left forefinger and thumb, using the slightest possible pressure to the testis so as not to deform the organ. No effort was made to stretch the skin of the scrotum. The volume (V) in cc of a single testicle was calculated using the formula for a spheroid of revolution, $V = 4/3\ \pi\ (a/2)\ (b/2)\ (c/2)\ (1/1000)$, where a, b, and c are the three dimensions in mm [27–29].

RESULTS

The results given in table 1 include the mean, standard deviation, and the minimum and maximum values for each of the eight measurements in each of the six groups. The right and left volumes were subjected to an analysis of variance in which the XYYs and their two matched controls are contained in one set, and the XXYs and their controls are regarded as a second matched set. A single subject was measured on both right and left sides, this being regarded as repeated measures.* (A similar analysis of variants

* Because it is known that designs of this sort are positively biased by violations of the assumptions placed on the variance-covariance matrix, conservative tests have been performed, where appropriate, following the $\tilde{\epsilon}$ procedure described by Huynh [31]. The adjusted df for the conservative tests are reported in parentheses in the analysis summary tables, and all reported significance levels reflect the conservative tests.

TABLE 1

TESTICULAR MEASUREMENTS IN XYY, XXY, AND XY GROUPS

	LEFT			RIGHT		
	Mean	SD	Range	Mean	SD	Range
XYY Set:						
Height (mm):						
XYY	41.50	4.7	34–51	41.08	5.1	31–49
C-1	44.42	3.7	38–50	42.58	5.7	27–50
C-2	42.17	4.3	36–52	45.17	5.1	36–55
Small width (mm):						
XYY	23.17	3.4	20–32	25.17	2.1	22–30
C-1	23.42	2.9	20–30	25.00	4.5	15–32
C-2	22.83	3.2	17–26	26.25	3.2	21–34
Large width (mm):						
XYY	29.92	4.0	24–40	29.83	3.2	25–35
C-1	32.25	3.6	26–40	31.25	3.7	22–37
C-2	31.08	4.0	24–36	31.42	3.0	28–39
Volume (cc):						
XYY	15.62	6.4	8.97–34.18	16.46	4.6	10.97–26.94
C-1	17.83	4.7	12.34–27.65	18.20	6.2	4.67–28.52
C-2	16.12	5.1	8.97–24.07	20.10	7.0	11.88–38.19
XXY Set:						
Height (mm):						
XXY	25.07	3.9	20–33	25.86	5.1	18–36
C-1	42.00	3.9	37–52	41.62*	5.1	30–50
C-2	42.36	3.4	38–48	44.57	4.2	37–55
Small width (mm):						
XXY	13.07	2.5	10–18	12.71	2.8	9–17
C-1	22.07	3.0	16–27	24.69*	3.2	20–31
C-2	24.36	3.0	20–30	27.07	3.0	22–32
Large width (mm):						
XXY	17.86	4.6	9–30	17.36	4.2	12–24
C-1	31.14	3.0	26–35	29.77*	3.3	23–34
C-2	31.86	2.9	27–37	30.93	3.2	26–36
Volume (cc):						
XXY	3.33	2.1	1.04–9.33	3.23	1.7	1.02–6.33
C-1	15.21*	4.4	8.71–23.82	16.58*	5.6	7.23–27.59
C-2	17.34	3.7	11.31–24.57	19.97	5.7	11.08–33.18

* Right testis of one XXY-control-1 subject had been surgically removed. Means shown here are for 13 subjects with complete data. Prior to ANOVAs, missing values were conservatively replaced by respective means based on remaining 77 study participants.

(ANOVA) is illustrated by Winer [30], pp. 539–559.)

Table 2 summarizes the analysis of variance on testicular volumes. The nonsignificant sides × groups interaction focuses interest on the significant groups main effect ($P < 10^{-10}$). The analysis of simple effects clarifies the interpretation of the groups effect. In particular, the simple XYY analysis produced a nonsignificant F ratio. The XYYs' testicular volumes do *not* differ from those of their XY controls. However, the simple XXY analysis produced a significant group effect ($P < 10^{-11}$), which can be further partitioned to contrast the XXY group with the average of its two control groups (contrast 1). The resulting F ratio is highly significant ($P < 10^{-12}$, two-tailed), indicating that the XXY group differs from its control groups. The minimum volume of a single testicle in the XXYs was 1.0 cc on both sides, and the maximum volume of a single testicle of the XXYs was 6.3 and 9.3 cc, right and left sides, respectively.

TABLE 2

ANALYSIS OF VARIANCE ON TESTICULAR VOLUMES

Source	df	Mean square	*F* ratio	*P*
Groups in set*	4	$.9528 \times 10^{9}$	24.01	$.5999 \times 10^{-10}$
Simple XYY groups	2	$.3280 \times 10^{8}$	.83	.4438
Contrast 1†	1	$.6547 \times 10^{8}$	1.65	.2052
Contrast 2‡	1	$.1165 \times 10^{6}$	.00	.9570
Simple XXY groups	2	$.1872 \times 10^{8}$	47.18	$.4654 \times 10^{-11}$
Contrast 1†	1	$.3633 \times 10^{10}$	91.53	$.8975 \times 10^{-12}$
Contrast 2‡	1	$.1128 \times 10^{9}$	2.84	.0983
Subjects × groups in set	48	$.3969 \times 10^{8}$	...	...
Side§	1	$.8794 \times 10^{8}$	21.30	$.1103 \times 10^{-3}$
Set × side	1	$.1756 \times 10^{7}$	.43	.5204
Subjects × side in set	24	$.4128 \times 10^{7}$	...	...
Side × groups in set‖	4(3)#	$.1810 \times 10^{8}$	1.59	.2072
Subjects × side × groups in set	48(39)	$.1138 \times 10^{8}$	...	...
Set	1	$.8947 \times 10^{9}$	22.83	$.7294 \times 10^{-4}$
Subjects in set	24	$.3918 \times 10^{8}$	...	...

* Huynh $\tilde{\epsilon} = 1.0$.
† Contrast 1 compares abnormal group to combined control groups.
‡ Contrast 2 compares control-1 to control-2.
§ Huynh $\tilde{\epsilon} = 1.0$.
‖ Huynh $\tilde{\epsilon} = .80$.
Adjusted df in parentheses.

Contrast 2 compares control-1 to control-2 in the XXY set, but, as expected, the resulting *F* ratio is not significant.

The analysis in table 2 also allows a test of right vs. left volumes. The side effect is significant ($P < 10^{-3}$, two-tailed) and can be interpreted directly since there is no significant sets × sides interaction. The average means across all 78 subjects are 14.05 cc on the left side and 15.55 cc on the right.

Table 3 summarizes a similar analysis of variance on testicular shapes, using six measures for each subject (height and small and large widths for both right and left sides). The significant measures × groups interaction ($P < 10^{-4}$) indicates that the testicles are *not* of the same shape in all groups. The interaction effect can be partitioned into a simple XYY interaction, which is not significant, and into a simple XXY interaction, which is significant ($P < 10^{-5}$). This simple XXY interaction can be further partitioned to obtain contrast 1, which compares the shape of the testes of the XXY group to the average shape of its two control groups. This contrast 1 is highly significant ($P < 10^{-6}$), indicating that the XXYs have testes of a shape different from their XY controls. Inspection of the mean heights and widths (table 1) shows that height contributes a greater proportion to XXY volume than it does to control volumes.

DISCUSSION

From 1961 through 1975, 13 of the 17 publications noting testicular condition in XYYs cited abnormalities; for example, total absence of the testes, varying degree of hypogonadism, and abnormally large testes (as large as 100 cc). However, most reports suffered from ascertainment bias. The search for 47,XYY subjects was often restricted to maximum security hospitals, prisons, institutions for the mentally

TABLE 3

ANALYSIS OF VARIANCE ON TESTICULAR SHAPES

Source	df	Mean square	*F* ratio	*P*
Measures × groups in set*	20(14)†	25.72	3.66	$.2531 \times 10^{-4}$
Simple XYY interaction	10(7)	13.16	1.87	.0697
Contrast 1‡	5(4)	8.29	1.18	.3218
Contrast 2§	5(4)	18.03	2.56	.0402
Simple XXY interaction	10(7)	38.27	5.44	$.2926 \times 10^{-5}$
Contrast 1‡	5(4)	68.41	9.72	$.4167 \times 10^{-6}$
Contrast 2§	5(4)	8.13	1.16	.3323
Subjects × measures × groups in set	240(170)	7.03	...	...
Measures‖	5(4)	$.4824 \times 10^{4}$	888.76	$< 10^{-12}$
Set × measures	5(4)	23.06	4.25	$.3344 \times 10^{-2}$
Subjects × measures in set	120(93)	5.43	...	...
Groups in set #	4	$.2805 \times 10^{4}$	50.61	$< 10^{-10}$
Subjects × groups in set	48	55.43	...	...
Set	1	$.2561 \times 10^{4}$	51.30	$.2108 \times 10^{-6}$
Subjects in set	24	49.92	...	...

* Huynh $\tilde{\epsilon} = .71$.
† Adjusted df in parentheses.
‡ Contrast 1 compares abnormal group to combined control groups.
§ Contrast 2 compares control-1 to control-2.
‖ Huynh $\tilde{\epsilon} = .78$.
\# Huynh $\tilde{\epsilon} = 1.0$.

subnormal, and hospitals for psychiatric patients. Examinations were rarely performed by "blind" examiners, and objective measurements were not always reported.

The present study was designed to avoid as many of these criticisms as possible, being an unbiased survey of a well-defined population. Testicular examination of the subjects was performed by a single examiner, in a double-blind design, using objective measures as part of a structured procedure.

No significant differences in testicular volume or shape could be demonstrated among the XYY group and its two XY control groups. The mean height and volume corresponded closely to those found by several other authors studying the testicular size of normal populations or normal male patients (table 4). This indicates that previous incidental reports of testicular size in 47,XYY males reflect biased selection of subjects from certain population groups, that is, subjects exhibiting a higher degree of abnormality, more than they reflect accurate descriptions of 47,XYY men. Testes can be functionally abnormal even when of normal size [17, 39], but the need to insure the subjects' continued cooperation with other aspects of this study precluded testicular biopsies.

This study confirms previous ones which reported distinctly subnormal testicular size in 47,XXY males. The largest volume of a single XXY testicle in this sample was 9.3 cc, which compares well with the 8.4 cc found by Frøland [24]. It is double the maximum 4.5 cc reported by Stewart et al. [21]. The mean testicular height in this study was 25 mm, which corresponds with Stewart et al.'s reported range from 15 mm to 26 mm and with Ragoch's [22] finding in 100 "true" Klinefelter patients of a range from 16 mm to 22 mm.

The small size of the XXYs' testes in this study is in agreement with upper limits in

TABLE 4

MEAN TESTICULAR SIZE FOUND BY DIFFERENT AUTHORS

Author(s)	Year	Length (mm)	Wt or Vol
Spangaro [32]	1902	45	47 cc
Roessle & Roulet [33]	1932	43	34 g
Sand & Okkels [34]	1941	···	40 g
Olesen [35]	1948	···	36 g approx.
Lambert [36]	1951	···	40 cc
Hansen & With [28]	1952	···	35 cc
Tishler [37]	1971	43	···
Farkas [38]	1976	46	37 cc
Present study	1979	43	35 cc

the previous reports which drew their XXY subjects from special clinics for male hypogonadism with severe testicular defects. Since the subjects of this study were derived from a population survey, it seems likely that the average size of the testes of 47,XXY men, while distinctly subnormal, are nonetheless actually larger than previously believed.

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REFERENCES

1. SANDBERG AA, KOEPF GF, ISHIHARA T, HAUSCHKA TS: XYY human male. *Lancet* 2:488–489, 1961
2. DUNN HG, FORD DK, AUERSPERG N, MILLER JR: Benign congenital hypotonia with chromosomal anomaly. *Pediatrics* 28:578–591, 1961
3. COURT BROWN WM, HARNDEN DG, JACOBS PA, MACLEAN N, MANTLE DJ: Abnormalities of the sex chromosome complement in man. Medical Research Council, Special Report Series no. 305, Her Majesty's Stationary Office, London, 1964
4. BALODIMOS MC, LISCO H, IRWIN I, MERRILD W, DINGMAN JF: XYY karyotype in a case of familial hypogonadism. *J Clin Endocrinol* 26:443–452, 1966
5. WILTON E, LEVER A: XYY male. *S Afr Med J* 41:284–286, 1967
6. THORBURN MJ, CHUTKAN W, RICHARDS R, BELL R: XYY sex chromosomes in a Jamaican with orthopaedic abnormalities. *J Med Genet* 5:215–219, 1968
7. CARAKUSHANSKY G, NEU RL, GARDNER LI: XYY with abnormal genitalia. *Lancet* 2:1144, 1968
8. DODSON WE, AL-AISH MS, ALEXANDER DF: Cytogenetic survey of XYY males in two juvenile court populations. *J Med Genet* 9:287–288, 1972
9. ZEUTHEN E, NIELSEN J, YDE H: XYY males found in a general male population. *Hereditas* (Lund) 74:283–290, 1973
10. NIELSEN J, CHRISTENSEN A-L: Thirty-five males with double Y chromosome. *Psychol Med* 4:28–37, 1974
11. SCHLEGEL H-J, SCHÖNWETTER HP, LANGENBECK U: Beitrag zur Klinik und Psychopathologie der XYY-Konstitution. *Fortschr Neurol Psychiatr* 43:305–312, 1975
12. FORSSMAN H, WAHLSTRÖM J, WALLIN L, ÅKESSON HQ: *Males with Double Y-Chromosomes*. Stockholm, Scand Univ Books, 1975
13. RAINER JD, ABDULLAH S, JARVIK LF: XYY karyotype in a pair of monozygotic twins. *Br J Psychiatry* 120:543–548, 1972

14. GUSTAVSON K-H, VERNEHOLT J: The XYY syndrome in a prepubertal boy. *Hereditas* (Lund) 60:264–266, 1968
15. NIELSEN J: Klinefelter's syndrome and the XYY syndrome. *Acta Psychiatr Scand* [Suppl] 209:1–353, 1969
16. BAGHDASSARIAN A, BAYARD F, BORGAONKAR DS, ARNOLD EA, SOLEZ K, MIGEON CJ: Testicular function in XYY men. *Johns Hopkins Med J* 136:15–24, 1975
17. SKAKKEBÆK NE: Kvantitative Studier af det Germinative Epithel i den Humane Testis. *Foreningen af Danske Lægestuderendes Forlag (Copenhagen)* 1–111, 1974
18. PLUNKETT ER, BARR ML: Testicular dysgenesis. *Lancet* 2:853–857, 1956
19. JACOBS PA, STRONG JA: A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 183:302–303, 1959
20. KLINEFELTER HF JR, REIFENSTEIN EC, ALBRIGHT F: Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol* 2:615–627, 1942
21. STEWART JSS, MACK WS, GOVAN ADT, FERGUSON-SMITH MA, LENNOX B: Klinefelter's syndrome. Clinical and hormonal aspects. *Q J Med* (N. S. 28) 112:561–572, 1959
22. RABOCH J: A clinical study of 100 chromatin-positive men. *Fertil Steril* 15:331–337, 1964
23. NIELSEN J: Gender role-identity and sexual behaviour in persons with sex chromosome aberrations. *Dan Med Bull* 19:269–275, 1972
24. FRØLAND A: Klinefelter's syndrome. *Dan Med Bull* [*Suppl*] 16:1–108, 1969
25. WITKIN HA, MEDNICK SA, SCHULSINGER F ET AL.: Criminality in XYY and XXY men. *Science* 193:547–555, 1976
26. PHILIP J, LUNDSTEEN C, OWEN D, HIRSCHHORN K: The frequency of chromosome aberrations in tall men with special regard to 47,XYY and 47,XXY. *Am J Hum Genet* 28:404–411, 1976
27. HANSEN PF: *"Acid" Prostate Phosphatase and Production of Testis Hormone in Man.* Copenhagen, Munksgaard, 1949
28. HANSEN PF, WITH TK: Clinical measurements of the testes in boys and men. *Acta Med Scand* [*Suppl*] 266,142:457–465, 1952
29. PRADER A: Testicular size: assessment and clinical importance. *Triangle* 7:240–243, 1966
30. WINER BJ: *Statistical Principles in Experimental Design,* 2nd ed. New York, McGraw-Hill, 1971
31. HUYNH H: Some approximate tests for repeated measurement designs. *Psychometrika* 43:161–175, 1978
32. SPANGARO 1902, cit. e LAMBERT B: The frequency of mumps and mumps orchitis. *Acta Genet Stat Med* [*Suppl*] 1,2:1–166, 1951
33. ROESSLE & ROULET 1932, ibid.
34. SAND K, OKKELS H: Über die Struktur des Hodens bei gesetzlich kastrierten Personen. *Acta Pathol Microbiol Scand* 18:437–438, 1941
35. OLESEN H: *Morfologiske Sperma- og Testisundersøgelser.* Copenhagen, Munksgaard, 1948
36. LAMBERT B: The frequency of mumps and mumps orchitis. *Acta Genet Stat Med* [*Suppl*] 1,2:1–166, 1951
37. TISHLER PV: Diameter of testicles. *N Engl J Med* 285:1489, 1971
38. FARKAS LG: Basic morphological data of external genitals in 177 healthy Central European men. *Am J Phys Anthropol* 34:325–328, 1976
39. SKAKKEBÆK NE, ZEUTHEN E, NIELSEN J, YDE H: Abnormal spermatogenesis in XYY males. *Fertil Steril* 24:390–395, 1973